

Letters to the Editor

Cancers of the Nasopharynx and Oropharynx and Formaldehyde Exposure

SIR: Rats exposed to formaldehyde develop cancers of the nasal cavity, the site of first exposure among these nose-breathing animals. Among nose and mouth breathers such as humans, both the nasal and buccal-pharyngeal cavities come into direct contact with formaldehyde. Among industrial workers, however, mouth breathing may be more prominent because of physical exertion or in avoidance to the irritating odor of formaldehyde. In previous cohort studies of formaldehyde-exposed groups, however, there were no excesses of nasal cancer¹ and the results for oral cancer have been mixed.¹⁻⁵

We recently reported a mortality study of industrial workers exposed to formaldehyde.⁶ Although in the aggregate there was no excess risk of cancer associated with formaldehyde exposure, there were excesses for certain sites, including the lung, nasopharynx, and oropharynx. In the absence of a dose gradient for these tumors, a causal relation with formaldehyde exposure appeared unlikely at the levels and in the manner experienced by these workers. Further analyses have been carried out, however, to clarify the excess mortality from cancers of the nasopharynx and oropharynx, sites of immediate contact for humans.

Among white men in our study, 7 died from cancer of the nasopharynx and 5 from cancer of the oropharynx. Four of the nasopharyngeal and 2 oropharyngeal cancers occurred among individuals who worked during the 1950's in a single plant, thus suggesting some unique workplace exposure. This plant produces molding compounds, which is a dusty operation.

Another case of nasopharyngeal cancer and 1 of oropharyngeal cancer were also exposed to particulates, but in other plants. We analyzed the mortality from these cancers by formaldehyde and particulate exposure (table 1). For persons exposed to particulates, the risk of death from cancer of the nasopharynx increased with cumulative exposure to formaldehyde from a standardized mortality ratio (SMR) of 192 for <0.5 ppm-years to 403 for 0.5-5.5 ppm-years and to 746 for ≥5.5 ppm-years. This trend was not statistically significant. No such trend, however, was seen among workers not exposed to particulates. Cumulative exposure combines intensity and duration, and both appeared important in our study. Among the 5 persons with nasopharyngeal cancer and particulate exposure, there was a trend with duration; and all held jobs that had hourly excursions exceeding 4.0-ppm formaldehyde exposure. For oropharyngeal cancer, there was no trend in the SMRs by cumulative exposure to formaldehyde, regardless of particulate-exposure status.

Although the numbers are small and the trend in the SMRs with cumulative exposure are not statistically significant, the pattern for nasopharyngeal cancer suggests that simultaneous exposure to formaldehyde and particulates may be a risk factor for this tumor. The finding is generally consistent with case-control studies of nasopharyngeal cancer where relative risks from two-

fold to sevenfold have been reported among persons exposed to dust and smoke.^{7,8}

It is possible that the dose gradient observed for formaldehyde is only a surrogate for a gradient in the particulate levels (which were not measured in our study). We tend to think this possibility is not the case, however, since particulate exposures for these subjects were to dusts from molding compound operations, which probably contained free formaldehyde. Inhalation of these particulates may have, therefore, resulted in a heavier delivered dose than indicated by the formaldehyde exposure levels estimated for these workers.

Despite small numbers, the dose-dependent association of nasopharyngeal cancer with exposure to formaldehyde and particulates deserves further investigation through case-control studies, where the influence of formaldehyde and particulates may be evaluated with more statistical power than by standard cohort studies.

AARON BLAIR⁹

PATRICIA A. STEWART

ROBERT N. HOOVER

JOSEPH F. FRAUMENI, JR.

Epidemiology and Biostatistics Program

Division of Cancer Etiology

National Cancer Institute

National Institutes of Health

Public Health Service

U.S. Department of Health and Human Services

Bethesda, Maryland 20892

JUDY WALRATH

MAUREEN O'BERG

E. I. du Pont de Nemours & Co., Inc.

Wilmington, Delaware 19898

WILLIAM GAFFEY

Monsanto Co.

St. Louis, Missouri 63166

¹ Consensus Workshop on Formaldehyde. Report on the consensus workshop on formaldehyde. *Environ Health Perspect* 1984; 58:323-381.

² ACHESON ED, GARDNER MJ, PANNETT B, et al. Formaldehyde in the British chemical industry. *Lancet* 1984; 1:611-616.

³ PARTANEN T, KAUPPINEN T, NURMINEN M, et al. Formaldehyde exposure and respiratory and related cancers. *Scand J Work Environ Health* 1985; 11:409-415.

⁴ LIEBLING T, ROSENMAN KD, PASTIDES H, et al. Cancer mortality among workers exposed to formaldehyde. *Am J Ind Med* 1984; 5:423-428.

⁵ STAYNER L, SMITH AB, REEVE G, et al. Proportionate mortality study of workers in garment industry exposed to formaldehyde. *Am J Ind Med* 1986; 7:229-240.

⁶ BLAIR A, STEWART P, O'BERG M, et al. Mortality among industrial workers exposed to formaldehyde. *JNCI* 1986; 76:1071-1084.

⁷ ARMSTRONG RW, ARMSTRONG MJ, YU MC, et al. Salted fish and inhalants as risk factors for nasopharyngeal carcinoma in Malaysian Chinese. *Cancer Res* 1983; 43:2967-2970.

⁸ HENDERSON BE, LORICE E, JING JS, et al. Risk factors associated with nasopharyngeal carcinoma. *N Engl J Med* 1976; 295:1101-1106.

⁹ Address reprint requests to Dr. Blair, Landow Building, Room 4C16, National Institutes of Health, Bethesda, MD 20892.

TABLE 1.—SMRs for cancer of the nasopharynx and oropharynx among white men by cumulative exposure to formaldehyde and in presence or absence of particulates^a

Site and particulate category	Cumulative exposure at ppm-yr: ^b											
	0			<0.5			0.5-5.5			≥5.5		
	OBS	EXP	SMR	OBS	EXP	SMR	OBS	EXP	SMR	OBS	EXP	SMR
Nasopharynx												
Particulates	0	0	—	1	0.5	192	2	0.5	403	2	0.3	746
No particulates	1	0.2	532	1	0.2	416	0	0.3	—	0	0.2	—
Oropharynx												
Particulates	0	0	—	3	0.7	457	0	0.7	—	0	0.4	—
No particulates	0	0.2	—	1	0.3	354	1	0.4	264	0	0.3	—

^a $P > .05$ for all tests for trend.^b OBS=observed; EXP=expected.

SIR: We have reviewed the Blair et al. letter, which reexamines a nasopharyngeal cancer (NPC) mortality excess originally presented in an earlier study.¹ In their reexamination the authors conclude: "the pattern for nasopharyngeal cancer suggests that simultaneous exposure to formaldehyde and particulates may be a risk for this tumor."² We are currently reanalyzing all data in the earlier study to assess the validity of this conclusion. We have four major concerns that lead us to question the author's² latest conclusions.

These concerns over Blair's study² are the inconsistency of the relationship between NPC with formaldehyde and particulate exposure, the cursory treatment of particulates (in Blair's earlier study¹), the extremely short duration of employment of some of the decedents, and the use of indirect standardization to compare exposure groups.

One important criterion for establishing a valid epidemiologic association is the consistency of the relationship between the agent and the effect. There are three levels at which the NPC association of the authors² is inconsistent. No other study of workers exposed to formaldehyde and particulates has identified an excess of NPC.³⁻⁷ Second, only a single plant of the 10 plants in the study² had an excess of NPC. Of the 5 NPCs among persons exposed to formaldehyde and particulates, 4 occurred at our plant. If NPC were associated with formaldehyde and particulates, one would expect to find a consistent pattern of NPC excesses in other plants in the study having similar exposures. NPC levels for the other nine plants are as expected.

Third, the 4 NPC cases in our plant did not occur among persons known to have had the highest exposure to formaldehyde and particulates. The highest exposures to formaldehyde and particulate occurred prior to 1946, at which time major engineering controls were introduced. The 4 cases in our plant occurred among persons who were hired between 1949 and 1955. Among the 931 persons employed prior to 1946, no NPC has occurred. Latency for this group is 40 years or more. Furthermore, an ongoing follow-up study initiated in March 1986 has not identified any NPC among employees hired after 1955. These persons worked in the same conditions as

the 4 NPC cases, because formaldehyde-particulate levels were virtually the same from 1946 to mid-1970.

Our second major concern is the cursory treatment of particulates in the study with regard to definition, measurement, and use in the reanalysis. Particulates are broadly defined as solid formaldehyde, formaldehyde containing resin, molding compound particulate, or any other particulate onto which formaldehyde gas may be absorbed.⁸ This definition is too all encompassing to even begin analysis of particulate effects. Analysis becomes even more unreliable because of the lack of particulate measurements and information regarding par-

¹ BLAIR A, STEWART P, O'BERG M, et al. Mortality among industrial workers exposed to formaldehyde. JNCI 1986; 76:1071-1084.

² BLAIR A, STEWART PA, HOOVER RN, et al. Letter to the Editor: Cancers of the nasopharynx and oropharynx and formaldehyde exposure. JNCI 1987; 78:191-192.

³ ACHESON ED, BARNES HR, GARDNER MJ, et al. Formaldehyde in the British chemical industry: An occupational cohort study. Lancet 1984; 1:611-616.

⁴ BERTAZZI PA, ZOCCHETTI C, PESATORI A, et al. Mortality of workers exposed to formaldehyde in resin manufacturing (abstract). III. International symposium on epidemiology in occupational health, Dublin, Ireland, September 1984. In press.

⁵ LIEBLING T, ROSENMAN KD, PASTIDES H, et al. Cancer mortality among workers exposed to formaldehyde. Am J Ind Med 1984; 5:423-428.

⁶ MARSH GM. Proportional mortality patterns among chemical plant workers exposed to formaldehyde. Br J Ind Med 1982; 39:313-322.

⁷ WONG O. An epidemiologic mortality study of a cohort of chemical workers potentially exposed to formaldehyde, with a discussion on SMR and PMR. In: Gibson JE, ed. Formaldehyde toxicity. New York: Hemisphere Publ, 1983:256-272.

⁸ STEWART PA, BLAIR A, CUBIT DA, et al. Estimating historical exposure to formaldehyde in a retrospective mortality study. Appl Ind Hyg 1986; 1:34-41.

⁹ GILBERT ES. Some confounding factors in the study of mortality and occupational exposure. Am J Epidemiol 1982; 116:177-188.

¹⁰ HENDERSON BE, LOUIS E, SOOTHOO J, et al. Risk factors associated with nasopharyngeal carcinoma. N Engl J Med 1976; 295:1101-1106.

¹¹ ANDERSON S, AUQUIER A, HAUCH WW, et al. Statistical methods for comparative studies: Techniques for bias reduction. New York: Wiley, 1980.